Attachment A

Actual Causes of Death in the United States, 2000

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Context Modifiable behavioral risk factors are leading causes of mortality in the United States. Quantifying these will provide insight into the effects of recent trends and the implications of missed prevention opportunities.

Objectives To identify and quantify the leading causes of mortality in the United States.

Design Comprehensive MEDLINE search of English-language articles that identified epidemiological, clinical, and laboratory studies linking risk behaviors and mortality. The search was initially restricted to articles published during or after 1990, but we later included relevant articles published in 1980 to December 31, 2002. Prevalence and relative risk were identified during the literature search. We used 2000 mortality data reported to the Centers for Disease Control and Prevention to identify the causes and number of deaths. The estimates of cause of death were computed by multiplying estimates of the cause-attributable fraction of preventable deaths with the total mortality data.

Main Outcome Measures Actual causes of death.

Results The leading causes of death in 2000 were tobacco (435000 deaths; 18.1% of total US deaths), poor diet and physical inactivity (400000 deaths; 16.6%), and alcohol consumption (85000 deaths; 3.5%). Other actual causes of death were microbial agents (75000), toxic agents (55000), motor vehicle crashes (43000), incidents involving firearms (29000), sexual behaviors (20000), and illicit use of drugs (17000).

Conclusions These analyses show that smoking remains the leading cause of mortality. However, poor diet and physical inactivity may soon overtake tobacco as the leading cause of death. These findings, along with escalating health care costs and aging population, argue persuasively that the need to establish a more preventive orientation in the US health care and public health systems has become more urgent.

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IN A SEMINAL 1993 ARTICLE, McGinnis and Foege[1] described the major external (nongenetic) modifiable factors that contributed to death in the United States and labeled them the "actual causes of death." During the 1990s, substantial lifestyle pattern changes may have led to variations in actual causes of death. Mortality rates from heart disease, stroke, and cancer have declined.[2] At the same time, behavioral changes have led to an increased prevalence of obesity and diabetes.[3]

Most diseases and injuries have multiple potential causes and several factors and conditions may contribute to a single death. Therefore, it is a challenge to estimate the contribution of each factor to mortality. In this article, we used published causes of death reported to the Centers for Disease Control and Prevention (CDC) for 2000, relative risks (RRs), and prevalence estimates from published literature and governmental reports to update actual causes of death in the United States—a method similar to that used by McGinnis and Foege.

METHODS

Our literature review used a MEDLINE database search of English-language articles that identified epidemiological, clinical, and laboratory studies linking risk behaviors and mortality. Our search criteria were to include all articles including the following key words: *mortality, smoking, physical activity, diet, obesity, alcohol, microbial agents, toxic agents, motor vehicle, firearms, sexual behavior, illicit drug use.* Our search allowed for words with similar meaning to be included (ie, exercise as well as physical activity). The search was initially restricted to articles published during or after 1990, but we later included relevant articles published in 1980 to December 31, 2002 (search strategies are available from the authors on request). For each risk factor, we used the prevalence and RR identified by the literature search. To identify the causes and number of deaths, we used mortality data reported in 2000 to the CDC.[4] We used no unpublished information or data.

We used the following formula to calculate attributable fractions for each disease: $[(P_0+\Sigma P_i\ (RR_i))-1]/[P_0+\Sigma P_i\ (RR_i)]$, in which P_0 is the percentage of individuals in the United States not engaging in the risk behavior, P_i is the per-

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centage engaging in separate categories of the risk behavior, and RR_i is the RR of death for each separate category relative to none. For instance, in the case of smoking, P_0 is the percentage of persons who never smoked, P_1 is the percentage of former smokers, P_2 is the percentage of current smokers, RR_1 is the RR of a certain type of death for former smokers compared with those who never smoked, and RR_2 is the RR of death for current smokers compared with those who never smoked. We then multiplied estimates of the cause-attributable fraction of preventable deaths by total mortality data. Whenever possible, we used RRs of death and mortality data by other variables such as age, sex, and race.

We estimated ranges for our estimated number of deaths by using the smallest and highest RRs and their boundaries when available. When data were available, we used specific underlying causes of death in deriving some of our estimates (ie, firearms, motor vehicles, and illicit drug use). Further details of these methods may vary due to availability of data and are presented in each section below. We used SAS (version 8.2, SAS Institute Inc, Cary, NC) and SUDAAN (version 8.0, Research Triangle Institute, Research Triangle Park, NC) statistical software.

RESULTS

The number of deaths in the United States in 2000 was 2.4 million, which is an increase of more than 250 000 deaths in comparison with the 1990 total, due largely to population growth and increasing age.[2,4] Leading causes of death were diseases of the heart (710 760), malignant neoplasms (553 091), and cerebrovascular diseases (167 661) (TABLE 1).

Table 1. Leading Causes of Death in the United States in 2000*

Cause of Death	No. of Deaths	Death Rate per 100 000 Population
Heart disease	710 760	258.2
Malignant neoplasm	553 091	200.9
Cerebrovascular disease	167 661	60.9
Chronic lower respiratory tract disease	122 009	44.3
Unintentional injuries	97 900	35.6
Diabetes mellitus	69 301	25.2
Influenza and pneumonia	65 313	23.7
Alzheimer disease	49 558	18
Nephritis, nephrotic syndrome, and nephrosis	37 251	13.5
Septicemia	31 224	11.3
Other	499 283	181.4
Total	2 403 351	873.1

*Data are from Minino et al.[1]

Tobacco

We used methods and software used in previous CDC reports to compute the annual smoking-attributable mortality for 2000.[5,6] As in previous reports, we used RRs for each cause of death from the American Cancer Society's Cancer Prevention Study II[7] and included deaths due to secondhand smoking.

We used data from the Behavioral Risk Factor Surveillance System (BRFSS), a cross-sectional telephone survey conducted by state health departments with the CDC's assistance, to determine changes in US smoking prevalence from 1995-1999 to 2000. A detailed description of survey methods is available elsewhere.[8] A slight decline in smoking was observed from 1995-1999 to 2000. The prevalence of smoking in 1995-1999 was 22.8% for current smokers (males: 25.1%; females: 20.6%), 24.1% for former smokers (males: 28.3%; females: 20.3%), and 53.1% for never-smokers (males: 46.5%; females: 59.2%). In 2000, these estimates were 22.2% for current smokers (males: 24.1%; females: 20.5%), 24.4% for former smokers (males: 28.3%; females: 20.7%), and 53.4% for never-smokers (males: 47.6%; females: 58.8%).

We estimate that approximately 435 000 deaths were attributable to smoking in 2000, which is an increase of 35 000 deaths from 1990 (TABLE 2). This increase is due to the inclusion of 35 000 deaths due to secondhand smoking and 1000 infant deaths due to maternal smoking, which were not included in the article by McGinnis and Foege.[1]

Poor Diet and Physical Inactivity

To assess the impact of poor diet and physical inactivity on mortality, we computed annual deaths due to overweight.[9] Recent articles have reported that overweight increased in all segments of the US population.[10,11] To derive the attributable number of deaths due to overweight, we used estimates from the CDC's 1999 and 2000 National Health and Nutrition Examination Surveys.[12] We used the same procedure reported by Allison et al[13] to estimate annual overweight-attributable deaths. We used the body mass index (BMI) range of 23 to 25 as our reference category to match the method used by Allison et al. Body mass index is calculated as weight in kilograms divided by the square of the height in meters. Using data from the 1999 and 2000 National Health and Nutrition Examination Surveys, the percentages for BMI cut points were less than 23 (22.3%), 23 to less than 25 (15.09%), 25 to less than 26 (7.49%), 26 to less than 27 (7.36%), 27 to less than 28 (6.23%), 28 to less than 29 (6.30%), 29 to less than 30 (5.94%), 30 to 35 (16.95%), and more than 35 (12.62%).

We used hazard ratios reported previously[13] to recompute annual deaths for 6 major population-based studies. The mean estimate of the total number of overweight-attributable deaths in 2000 was 494 921. For the Alameda County Health Study, the estimated number of overweight-attributable deaths in 2000 was 567 683; Framingham Heart Study, 543 981; Tecumseh Community Health Study, 462,005; American Cancer Society Cancer Pre-

Table 2. Actual Causes of Death in the United States in 1990 and 2000

Actual Cause	No. (%) in 1990*	No. (%) in 2000
Tobacco	400 000 (19)	435 000 (18.1)
Poor diet and physical inactivity	300 000 (14)	400 000 (16.6)
Alcohol consumption	100 000 (5)	85 000 (3.5)
Microbial agents	90 000 (4)	75 000 (3.1)
Toxic agents	60 000 (3)	55 000 (2.3)
Motor vehicle	25 000 (1)	43 000 (1.8)
Firearms	35 000 (2)	29 000 (1.2)
Sexual behavior	30 000 (1)	20 000 (0.8)
Illicit drug use	20 000 (<1)	17 000 (0.7)
Total	1 060 000 (50)	1 159 000 (48.2)

*Data are from McGinnis and Foege.[1] The percentages are for all deaths.

vention Study I, 451 708; Nurses Health Study, 504 602; and the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study, 439 548.[14-19]

As in the study by Allison et al, the estimate for the attributable number of deaths for nonsmokers or never-smokers was higher than the estimate for the total because smoking is associated with both lower body weight and higher mortality. Also in 2000, the mean estimate of the total number of overweight-attributable deaths among nonsmokers or never-smokers was 543 797. For the Alameda County Health Study, the estimate of overweight-attributable deaths among nonsmokers or never-smokers was 639 026; Framingham Heart Study, 583 913; Tecumseh Community Health Study, 457 460; American Cancer Society Cancer Prevention Study I, 466 729; Nurses Health Study, 570 855; and the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study, 544 798. Our estimates indicate an increase of 76.6% over the 1991 estimate of overweight-attributable deaths, with more than 80% of excess deaths occurring among individuals with class 2 and 3 obesity.

The prevalence of overweight used in this study is based on data from 1999-2000. Because the effects of overweight on mortality may not appear until some years after a person becomes overweight, it is likely that the increase in prevalence of overweight in the 1990s overestimates the current actual number of deaths. However, the total number of deaths from the 1999-2000 data may well be the expected number of deaths in the next few years. Thus, we believe a more accurate and conservative estimate for overweight mortality in 2000 such as 385 000, which is the rounded average of 2000 and 1991 estimates (494 921 and 280 184).

Overweight would account for the major impact of poor diet and physical inactivity on mortality.[20] Diet may have a minor additional effect on mortality mainly from lack of certain essential nutrients.[21,22] Consumption of fruits and vegetables increased in the 1990s,[23] and fat intake as a percentage of calories declined.[24] Physical activity has increased slightly.[25] We estimate that poor diet and physical inactivity will cause an additional 15 000 deaths a year, although this too may be conservative. Nutritional deficiencies alone (*International Classification of Diseases, 10th Revision [ICD-10]* codes E40-E64) were reported as the causes of 4242 deaths in 2000.

We estimate that 400 000 deaths were attributable to poor diet and physical inactivity, an increase of one third from 300 000 deaths estimated by McGinnis and Foege,[1] and the largest increase among all actual causes of death. However, poor diet and physical inactivity could account for even more deaths (>500 000) when the 1999-2000 prevalence estimates of overweight have their full effect.

Alcohol Consumption

We used 2 large nationally representative surveys to determine US alcohol consumption. The National Health Interview Survey, a household survey that measured alcohol intake in 1999 and 2000, and the BRFSS, a telephone survey that measured alcohol intake in 1999.[8,26]

We used RRs from the Australian National Drug and Safety Report that were based on mortality rates derived from pooled data of several studies.[27,28] The RR values were 1.33 for hazardous drinking (4.01-6.00 drinks/d for males and 2.01-4.00 for females) and 1.47 for harmful drinking (≥6.01 drinks/d for males and ≥4.01 for females) in contrast to low levels of drinking (0.26-4.00 drinks/d for males and 0.26-2.00 for females) and abstinence (0-0.25 drinks/d for both males and females).

We used BRFSS data to compute the number of alcohol-attributable deaths for the US population aged 18 years or older. The BRFSS also asked questions about binge drinking (ie, ≥5 drinks per occasion). To account for the effect that respondents appeared not to include binge drinking in their reported regular drinking, we reran our analyses, adding 5 drinks per binge occasion to average drinks per day. The total number of deaths attributable to alcohol was 103 350.

We also used 3 other recent studies to estimate alcohol-attributable mortality. Two studies were based on the National Health Interview Survey[29,30] and the National Alcohol Survey.[31] Using all-cause mortality and RRs from these studies, we estimated approximately 60 000 deaths per year. This difference in number of deaths is mainly due to the fact that BRFSS respondents report a higher percentage of heavy drinking than do respondents in a household survey such as the National Health Interview Survey.

In another approach, we aggregated alcohol-related deaths from specified *ICD* codes that were summed to provide an overall estimate of deaths. In 2000, 18 539 deaths were reported as alcohol-induced (*ICD-10* codes F10, G31.2, G62.1, I42.6, K29.2, K70, R78.0, X45, X65). In addition, 16 653 persons were killed in alcohol-related crashes.[32]

We estimate another 34797 deaths in 2000 using BRFSS alcohol consumption data and disease-specific RRs from the Australian study for oropharyngeal, esophageal, liver, laryngeal, and female breast cancers; stroke; hypertensive heart disease; and other chronic liver disease and cirrhosis (*ICD-10* code K73-74). This totals to 69989 deaths in 2000 from these factors alone. In the Australian study, all-cause mortality was also higher than the summation of cause-specific mortality.

Total alcohol-attributable deaths would reach about 140000 if mortality among previous alcohol drinkers were included. It is unclear whether excess mortality among former alcohol drinkers is due to damage or illness from past alcohol consumption.

Taking these various numbers into account, our best estimate for total alcohol-attributable deaths in 2000 is approximately 85000, based on the conservative estimate from cause-specific deaths and the high estimate using all-cause mortality. This is a reduction of 15000 deaths from the 1990 estimates.

Microbial Agents

We excluded human immunodeficiency virus (HIV) from this category and included it with sexual behaviors to be consistent with the analysis by McGinnis and Foege.[1] In the past, infectious agents were the leading cause of mortality.[33] These agents still present a major threat to the nation's health and are associated with high morbidity.[34] Several improvements in the health system have led to a decline in mortality from infectious diseases. The increase in US immunization rates led to a decline in mortality from many vaccine-preventable diseases.[35-37] Several laws ensure this high immunization rate for children by requiring vaccination for school and day-care enrollment.[38] There also have been substantial improvements in sanitation and hygiene, antibiotics and other antimicrobial medicines, and hospital-infection control.[35]

In 2000, influenza and pneumonia accounted for 65313 deaths, septicemia for 31224, and tuberculosis for 776.[4] In general, mortality from infectious and parasitic diseases has declined since 1990.[33] Because pneumonia and septicemia occur at higher rates among patients with cancer, heart disease, lung disease, or liver disease, some of these deaths really are attributable to smoking, poor diet, and alcohol consumption.[39-43] We estimate that approximately 75000 deaths were attributable to microbial agents in 2000 from all *ICD-10* codes for infectious and parasitic mortality. The major cause of the decline was a decrease in deaths from influenza and pneumonia probably reflecting at least in part an increase in immunization in older adults against vaccine-preventable diseases. This contrasts with 90000 deaths attributed to microbial agents in 1990 estimates.

Toxic Agents

Estimating the number of deaths due to toxic agents is more challenging than any of the other risk factors due to limited published research and the challenges of measuring exposure and outcome. In the 1990s, many improvements were made in controlling and monitoring pollutants.[44] There is more systematic monitoring of pollutants at state and county levels, and exposure to asbestos, benzene, and lead have declined.[44] In fact, the US Environmental Protection Agency reported a decline of 25% from 1970 to 2001 in 6 principal air pollutants: carbon monoxide, lead, ozone, nitrogen dioxide, sulfur dioxide, and particulate matter.[45]

Toxic agents are associated with increased mortality from cancer, respiratory, and cardiovascular diseases.[46-49] We used the National Morbidity, Mortality, and Air Pollution Study to estimate mortality due to air pollution.[50] The study assessed the association between air pollution and mortality and morbidity in 90 cities in the United States. Only particulate matter (PM) was associated with a significant increase in mortality—an approximate 0.5% increase in total mortality for each 10-μ/m^3 increase in PM_{10}. Previous studies reported a range of 0.4% to 1% for that association.[51,52] We used 23.8 μ/m^3 as the daily average of PM_{10} concentration in 2000,[45] which results in an estimate of 24000 deaths per year (range, 22000-52000 deaths) from air pollution alone.

The National Institute for Occupational Safety and Health (NIOSH) estimates that about 113000 deaths are due to occupational exposure from 1968 to 1996.[53] The number of deaths caused by occupational exposure has declined during that period. In 1996, NIOSH estimated 3119 deaths from pneumoconiosis and 1176 from asbestosis. Although, particulate air pollution accounts for the majority (about 60%) of mortality related to toxic agents,[54] indoor air pollution, environmental tobacco smoke, radon, lead in drinking water, and food contamination are associated with increased mortality.[55,56] We estimate that toxic agents (excluding environmental tobacco exposure) were associated with 2% to 3.5% of total mortality in 2000. We estimate approximately 55000 deaths attributable to toxic agents in 2000. This estimate is our least certain of the various causes.

Motor Vehicles

Motor-vehicle crashes involving passengers and pedestrians resulted in 43354 deaths in 2000.[4] This decline from 47000 deaths in 1990 represents successful public health efforts in motor-vehicle safety.[57,58] Deaths from alcohol-related crashes declined from 22084 in 1990 to 16653 in 2000.[32] Major contributing factors include the use of child safety seats and safety belts,[59,60] decreases in alcohol-impaired driving,[61] changes in vehicle and highway design,[62,63] and national goals to reduce motor-vehicle–related mortality and injury.[64] We estimate that approximately 26500 deaths in 2000 were attributable to motor-vehicle crashes in which alcohol was not a factor. This is an increase of 1500 from the 1990 report because both estimates were not adjusted for the number of registered vehicles, number of crashes, nor miles of travel. We included alcohol-related deaths to stress that efforts to educate the public and enforce laws against driving while intoxicated have accounted for most of

the decline in deaths related to motor-vehicle crashes.

Firearms

Firearm-related incidents resulted in 28 663 deaths among individuals in the United States in 2000.[4] This is a decline from approximately 36 000 deaths in 1990. The largest declines were in deaths from homicides and unintentional discharge of firearms. In 2000, 16 586 deaths were due to intentional self-harm (suicide) by discharge of firearms (*ICD-10* codes X72-X74). Assault (homicide) by discharge of firearms (*ICD-10* codes X93-X95) resulted in 10 801 deaths. Unintentional discharge of firearms (*ICD-10* codes W32-W34) resulted in 776 deaths, while discharge of firearms, undetermined intent (*ICD-10* codes Y22-Y24), resulted in 230 deaths. The remaining 270 deaths were due to legal intervention (*ICD-10* code Y35). These numbers were ascertained from death certificate reports.

Sexual Behavior

Sexual behavior is associated with an increased risk of preventable disease and disability.[65] An estimated 20 million persons are newly infected with sexually transmitted diseases each year in the United States.[66,67] Mortality from sexually transmitted diseases is declining due to the availability of earlier and better treatment, especially for HIV.[67,68] In 2000, HIV disease (*ICD-10* codes B20-B24) resulted in 14 578 deaths. In 1990, HIV was the cause of 27 695 deaths for persons older than 13 years, indicating about a 48% decline in HIV mortality during the decade. Based on the sexual behavior–attributable fraction from the literature,[69-71] we estimate that 20 000 deaths (range, 18 000-25 000 deaths) in 2000 were due to sexual behavior—mainly HIV; other contributors were hepatitis B and C viruses and cervical cancer. The decline of 10 000 deaths from the 1990 estimates[1] was due to the decline in HIV mortality.

Illicit Use of Drugs

Illicit drug use is associated with suicide, homicide, motor-vehicle injury, HIV infection, pneumonia, violence, mental illness, and hepatitis.[27,28,72-77] An estimated 3 million individuals in the United States have serious drug problems.[78,79] Several studies have reported an undercount of the number of deaths attributed to drugs by vital statistics[80]; however, improved medical treatments have reduced mortality from many diseases associated with illicit drug use. In keeping with the report by McGinnis and Foege,[1] we included deaths caused indirectly by illicit drug use in this category. We used attributable fractions to compute the number of deaths due to illicit drug use.[27,28,81] Overall, we estimate that illicit drug use resulted in approximately 17 000 deaths in 2000, a reduction of 3000 deaths from the 1990 report.

Other Factors

Several other factors contribute to an increased rate of death. There are factors that we do not know of such as unknown pollutants or perhaps exposures that may cause a considerable number of deaths. Poverty and low education levels are associated with increased mortality from many causes,[82,83] partly due to differential exposure to the risks described above. However, controlling for differential exposure to risk factors is unlikely to explain the entire impact on mortality. Lack of access to proper medical care or preventive services is associated with increased mortality.[84] Biological characteristics and genetic factors also greatly affect risk of death.[85] In most studies we reviewed, low education levels and income were associated with increased risk of cardiovascular disease, cancer, diabetes, and injury. The Healthy People 2010 initiative has made the elimination of health disparities, especially racial and ethnic disparities, a primary goal.[86]

COMMENT

We found that about half of all deaths that occurred in the United States in 2000 could be attributed to a limited number of largely preventable behaviors and exposures. Overall, we found relatively minor changes from 1990 to 2000 in the estimated number of deaths due to actual causes. Our findings indicate that interventions to prevent and increase cessation of smoking, improve diet, and increase physical activity must become much higher priorities in the public health and health care systems.

The most striking finding was the substantial increase in the number of estimated deaths attributable to poor diet and physical inactivity. We estimate that roughly 400 000 deaths now occur annually due to poor diet and physical inactivity. The gap between deaths due to poor diet and physical inactivity and those due to smoking has narrowed substantially. Because rates of overweight increased rapidly during the 1990s, we used a conservative approach to make our estimates, accounting for the delayed effects of overweight on mortality. In addition, overweight lessens life expectancy.[87,88] However, it is clear that if the increasing trend of overweight is not reversed over the next few years, poor diet and physical inactivity will likely overtake tobacco as the leading preventable cause of mortality.

The most disappointing finding may be the slow progress in reducing tobacco-related mortality. A few states, notably California, have had major success in programs that led to reducing deaths from heart disease and cancer.[89] However, efforts in most other states are too recent or short-term to have a similar effect. In response to the increase in tobacco use among youth in the early 1990s, state and national tobacco-control efforts increased their focus on prevention of initiation and recognized the importance of cessation on reducing smoking-related deaths. Thus, most national and state efforts now address comprehensive program strategies.[90] Current tobacco-control efforts will also need strong cessation components to show a decline in tobacco deaths in a future assessment. Recent reports on the effects of telephone quit lines for smokers are encouraging.[91] On the other hand, large

state budget shortfalls are leading to large cuts in public health, with a corresponding diversion of resources from tobacco taxes and settlement dollars to cover deficits instead of tobacco-control programs.

Despite the call to action on these risk factors a decade ago, there has been little progress in reducing the total number of deaths from these causes. The progress that has occurred primarily involves actual causes of death that are less prominent. With the shift in the age distribution of the population, more adults now are in the age group at highest risk because of the cumulative effects of their behavior. The net effect is that both total deaths and total burden due to the actual causes have increased.

Our analyses have several limitations. Our study reported actual causes of mortality in the United States. However, these causes are also associated with a large morbidity burden. In addition to premature death, years of lost life, diminished productivity, and high rates of disability, decreased quality of life is also strongly associated with these actual causes. A recent World Health Organization report finds these actual causes of death to be the leading causes of total disease burden, not just mortality, in the developed world.[92] Because we used self-reported estimates for some risk behaviors, (ie, prevalence of alcohol intake) they may have been underestimated. Finally, using all-cause mortality may result in overestimates of the number of deaths from specific causes. In addition, if the effect of the risk factor is age-dependent, then age- and sex-specific estimates are preferable.

Our analyses did not assess the effect of genetics. Genetic factors have been associated with several diseases discussed herein.[93] Much of the impact of genetics is likely mediated through increased physical susceptibility to these behavioral and other modifiable risks. However, increases in obesity and diabetes cannot be due to widespread changes in the human genome over the last 10 years. Nevertheless, genetics offers great potential for treating and ameliorating risk. Identifying individuals at higher risk for a disease through genetic testing may promote lifestyle changes that can help prevent the onset of that disease.[93]

In this study we also did not examine the effects of high blood pressure and cholesterol or lipid profile on mortality, although some of the effects of these factors are meditated through poor diet and physical inactivity. These risk factors are common among adults in the United States. More than 30% of US adults have high blood pressure or high cholesterol.[94,95] Monitoring and controlling blood pressure and cholesterol is crucial to preventing premature mortality and morbidity.

One of the most difficult aspects of this analysis is that the attribution of the actual cause that led to death varies depending on perspective. We used similar methods to those used by McGinnis and Foege[1] to allow comparisons. We tried when possible to use RRs that are fully adjusted for other risk factors in our analyses, but possibly not eliminating duplicate attribution of causes. We also explicitly included some deaths in more than 1 category (eg, alcohol and motor vehicle crashes) when choosing another category seemed as though it might artificially constrain interpretation for future prevention programs.

In summary, smoking and the deaths attributed to the constellation of poor diet and physical inactivity currently account for about one third of all deaths in the United States. The rapid increase in the prevalence of overweight means that this proportion is likely to increase substantially in the next few years. The burden of chronic diseases is compounded by the aging effects of the baby boomer generation and the concomitant increased cost of illness at a time when health care spending continues to outstrip growth in the gross domestic product of the United States. In ancient times, Hippocrates stated that "the function of protecting and developing health must rank even above that of restoring it when it is impaired." The findings in this study argue persuasively for the need to establish a more preventive orientation in health care and public health systems in the United States.

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The Immediate vs the Important

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WHEN HIPPOCRATES OBSERVED THAT "PROTECTing and developing health must rank even above that of restoring it when it is impaired,"[1] he set a standard that is difficult to meet. One of the most difficult challenges is to ensure that the urgent does not crowd out the important. In health, this challenge is especially difficult because urgent matters can be so riveting. At the personal level, the presence of illness or injury often overpowers all other concerns, and the search for effective treatment often dominates all other pursuits. At the policy level, with 15% of the US gross domestic product devoted to health care,[2] medical care expenditures often drive decisions in which cost cutting is aimed first at discretionary investments, such as those in prevention and public health that offer the greatest prospects for overall health improvement. Hence, tools are needed to facilitate the gathering, analyzing, and reporting of data in a fashion that enables taking action not merely on the urgent but on issues most important to the health of a population.

In health, the most basic measure of importance is found in mortality tables—the registry of leading killers drawn from death certificate data. Despite the vital statistics system relying substantially on unverified physician reports that may be subject to various sources of bias, the results over time seem to be reasonably reflective of the dominant diagnoses at the time of death. For example, while the occasional suicide may be reported as an accidental death, a coronary heart disease death is likely to be accurately recorded, with reasonable indication of related conditions.

Every death has a definable history that usually can be traced back for decades and sometimes even for generations. Reporting of deaths, diseases, and disabilities in traditional diagnostic categories tends to obscure the importance of factors that often play determinant antecedent roles in the occurrence of the reported conditions. When it comes to ranking health problems and committing resources, attention seems more naturally drawn to the conditions most proximate to serious illness or death. For instance, a diagnosis of lung cancer draws interest and immediate concern because it is life-threatening and the certainty of its threat is unquestioned. Yet, nearly 9 times out of 10 lung cancer is merely the natural pathologic consequence of exposure to tobacco use, the single most prominent actual cause of the lung cancer. Ability to make progress on many of the key health challenges will remain constrained until focus and resources are directed to the root causes of these conditions.

Fortunately, much has been learned from research of the past generation about the factors leading to disease and injury and the magnitude of their contributions. The National Center for Health Statistics reports that the 10 leading causes of death in the United States in 2000 were heart disease, cancer, stroke, chronic lower respiratory tract disease, unintentional injury, diabetes, influenza and pneumonia, Alzheimer disease, nephritis, and septicemia.[3] The article by Mokdad and colleagues[4] in this issue of THE JOURNAL assesses these mortality data against current knowledge about the contributors to those conditions. The findings indicate that the leading actual causes of death for 2000 are tobacco, poor diet and physical inactivity, alcohol consumption, microbial agents, toxic agents, motor vehicles, firearms, sexual behaviors, and illicit use of drugs. Together, these causes accounted for approximately half of all deaths in 2000, with nearly two fifths attributable to the top 3: tobacco, poor diet and physical inactivity, and alcohol use. This analysis is an update of our earlier report,[5] which estimated the contributions of the actual causes of death in 1990. The order of the ranking for 2000 is similar to that for 1990, with an especially notable increase in those deaths attributable to poor diets and physical inactivity and a decline in deaths due to sexual behavior.

However, there are some differences in the approaches used in these 2 studies. First, the 1990 estimate for the impact of poor diet and physical inactivity was drawn from the range of estimates of the proportion of deaths from conditions related to these factors. In contrast, Mokdad et al used hazard ratios in an ambitious primary computation of annual deaths from the specific issue of obesity, rather than the full range of conditions related to diet and activity patterns. They added a correction of 15 000 for the non–obesity-related deaths but noted that this may be conservative. This estimate seems low, given the substantial number of cardiovascular and cancer deaths that may be attributable to the dietary and inactivity patterns of those who are not overweight or obese. Second, the 1990 assessment parsed the alcohol-related portion of motor vehicle fatalities and assigned these deaths to the alcohol category, which explains the higher 2000 number for motor vehicle deaths and lower number for alcohol deaths estimated by Mokdad et

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al. Third, where data and issues were most complicated (ie, diet and inactivity, toxic agents), the 1990 report used the lower bound of the estimates generated. Fourth, because the 1990 report generated estimates and not actual counts for several categories, a series of rounding rules were applied: numbers greater than 100 000 were rounded to the nearest 100 000; greater than 50 000, to the nearest 10 000; and less than 50 000, to the nearest 5000.

The information by Mokdad et al—in particular the modeling on the contributions of overweight and obesity—allows a stronger measure of confidence in reporting results at the midpoints of the estimate ranges for various categories. Specifically, the estimated range reported in our 1990 analysis for tobacco-attributable deaths was 257 000 to 468 000; for diet and activity patterns, it was 309 000 to 582 000; and for alcohol use, it was 67 000 to 107 000. Applying the same approach for deaths in the year 2000 gives approximate ranges of 340 000 to 642 000 for diet and activity patterns, 261 000 to 490 000 for tobacco, and 59 000 to 110 000 for alcohol. The estimates would suggest that diet/physical activity patterns are now in fact likely greater contributors to mortality than tobacco is (and, in retrospect, probably were in 1990) and are most likely increasing in their impact. Another important category not included in the 1990 or the 2000 articles is medical errors, which, according to the report from the Institute of Medicine, are estimated to account for 44 000 to 98 000 deaths annually.[6]

Despite these differences in analytic approaches, the observed trends in actual causes of death from 1990 to 2000 reflect several important conclusions and implications: that 3 causes identified—diet/activity patterns, tobacco, and alcohol—account for a substantial proportion of preventable deaths in the United States; that poor diets and physical inactivity are increasing rapidly as actual causes of deaths; that, despite highly visible concerns about newly emerging and the potential use of infectious agents as biological weapons, the death toll from infectious diseases continues to decline; and that the past decade has been one of substantial progress against HIV/AIDS in the United States, which appears in these estimates as reduced deaths from sexual behavior.

During this decade, a number of changes also occurred in terms of public attention and capacity for action. Public awareness has increased about obesity as a clear public health threat and about the importance of the fragile public health infrastructure as the frontline safeguard against bioterrorism, emerging infections, and environmental safety, and as the public leader of efforts that will foster health-promoting lifestyles. Advances in information technology over the last decade offer the prospects for earlier detection of problems, better targeting of efforts, and more reliable monitoring of public health results. Continued progress depends on strong and vibrant public health capacity, working with the solid support and involvement of medical practitioners to engage effectively the health needs of the communities they serve.

Several priorities seem clear at this point. Because a substantial proportion of early deaths among the US population is preventable through lifestyle change, the social commitment to making those changes possible must be enhanced considerably. Decisions about whether to smoke, how much to drink, how much and what kinds of food to consume, and activities in which to engage are the result of strong cultural and commercial signals. Unless strategies are specifically designed to address and improve the clarity and utility of these messages, US society will fall far short of the possible.

As analyses of the underlying causes of disease are refined, it is also important to better capture and apply evidence about the centrality of social circumstances to health status and outcomes. Although the data are still not crisp enough to quantify the contributions in the same fashion as many other factors, there is no question that from cradle to grave, interpersonal linkages matter. For instance, studies consistently have shown that infant nurturing enhances socialization and survival.[7] Prenatal home visits to at-risk mothers can reduce the likelihood of both risky health behaviors and criminal activity by the children some 15 years hence.[8] Adults, including older people, who are socially isolated have a 2- to 5-fold higher death rate than others.[9] Parsing the ways in which social factors affect and protect health status, and the magnitude of the impact for some populations, will help to heighten sensitivity to the issues and better target interventions.

Refining insights into the root causes of illness and injury, presenting those insights in a fashion that can motivate and guide effective action, and marshaling the effort to monitor the results of these actions will require steady improvement in the knowledge base. National leadership and commitment at the policy level, such as suggested by Mokdad and colleagues, is an important ingredient for progress. If the nation can heed the insights they share, acceleration of the attention and action necessary for progress ought to be anticipated. After all, "Wisdom is knowing what to do next. Virtue is doing it."[10]

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Modifiable Behavioral Factors as Causes of Death

To the Editor: Dr Mokdad and colleagues[1] reported that the leading cause of mortality in the United States is tobacco use, followed by poor diet/inactivity and alcohol use. I believe that the authors should also address the beneficial effects on mortality, if any, of these modifiable factors. Some may be beneficial in small quantities and may thus have a U-shaped relationship to mortality. One example is the well-documented beneficial effect of low levels of alcohol consumption on the health of populations with a high risk of cardiovascular disease.[2-4]

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To the Editor: Dr Mokdad and colleagues[1] reported that about one third of deaths in the United States are attributable to smoking and overweight. By calling attention to a predicted increase in health care costs secondary to these risk factors, the authors implied that prevention of these risk factors will save costs. They concluded that there is an urgent need to provide more prevention of these risk factors.

This conclusion seems premature, however. First, diseases such as depression and osteoarthritis are not listed among the leading causes of death but lead to considerable societal morbidity.[2] Hence, setting priorities only on the basis of mortality data can lead to bias. Second, I am not aware of evidence that primary or secondary prevention of overweight would reduce long-term costs. Primary prevention will waste money on some people who remain lean, while secondary prevention may waste money on the many people who resist changing their behavior. Furthermore, an increase in life expectancy may result in increased costs for diseases such as dementia.

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To the Editor: Dr Mokdad and colleagues[1] attributed 400 000 US deaths to obesity, just below the 435 000 they attributed to tobacco. The estimate for tobacco was achieved[2] by stratifying by cause of death, sex, and age, then adding up the resulting individual causes. The estimate for obesity does not account for important variables, particularly age and unmodifiable genetic factors.[3] Because the risk of dying because of obesity decreases at advanced age,[4] the authors should have taken this variable into account in the estimations. In addition, the population age distribution is now older than when these studies were performed, so applying unadjusted risk estimates to the current population overestimates the number of deaths.

We are also concerned that the authors provided no justification for adding 15 000 deaths for poor diet and physical inactivity. They provided no evidence to support the assumption that these deaths would occur beyond the direct effects of obesity per se. In contrast to this strategy in the case of obesity, the authors underestimated the number of deaths due to secondhand smoke. Their estimate of 35 000 deaths is the lower bound of the estimate for heart disease published by the California Environmental Protection Agency.[5] Using the mean estimates of deaths for heart disease, lung cancer, and sudden infant death syndrome would significantly increase the estimate of the number of deaths due to passive smoking.

Every premature death from tobacco is avoidable. While interventions such as eliminating sugared drinks in schools or increasing exercise might reduce the level of obesity,[6] a substantial fraction of obesity is due to genetics.[7] The authors acknowledged this fact but did not attempt to estimate its effect. Even if genetics accounted for only 20% of the obesity effect, the estimate of preventable deaths per year would be 80 000 fewer.

Given that the data necessary to do the obesity calculations with these adjustments are available, we request that Mokdad and colleagues provide these more accurate estimates.

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Letters Section Editor: Stephen J. Lurie, MD, PhD, Senior Editor.

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To the Editor: By focusing solely on behavioral factors as the underlying cause of deaths, Dr Mokdad and colleagues[1] may have perpetuated the argument that these preventable deaths are the individual's responsibility alone. By contrast, a growing body of research has reported significant relationships between health and a variety of social determinants, including income, race, ethnicity, sex, and occupation.[2,3] The relationship between health and these social determinants may not operate exclusively through differences in the prevalence of behavioral risk factors.[4]

For instance, people living in households with incomes of at least $25 000 live 3 to 7 years longer than those living in households with incomes of $10 000 or less.[2] Furthermore, poverty is a significant risk factor for obesity.[5] Paying more attention to social determinants of health does not obviate efforts to address behavioral risk factors but, instead, places some of the responsibility for improving the population's health on the efforts of government and society to improve social conditions for all.

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To the Editor: To compute the fraction of mortality attributed to specific behaviors relating to poor diet and overweight, Dr Mokdad and colleagues[1] estimated the annual deaths due to overweight. We do not understand the authors' conclusion that the "major impact of poor diet and physical inactivity" would be mediated by overweight, and we are puzzled by why they cited one of our articles[2] to support this assertion. We have 2 concerns about their approach.

First, the attributable risk of mortality due to poor diet and inactivity should be computed using population prevalence and relative risk data for each of these exposures, rather than using data for overweight as a surrogate indicator of these behaviors. As McGinnis and Foege[3] pointed out in their accompanying Editorial, "the 1990 estimate for the impact of poor diet and physical inactivity was drawn from the range of estimates of the proportion of deaths from conditions related to these factors." Thus, the assertion of Mokdad et al that deaths due to poor diet and inactivity have increased from 300 000 to 400 000 from 1990 to 2000 is inappropriate given the different approaches used to develop these 2 estimates.

Second, poor diet and physical inactivity are directly associated with risk of mortality, independent of body size and overweight. In their Table 2, Mokdad et al attributed 400 000 deaths to poor diet and inactivity. They indicated that 385 000 of these deaths were due to overweight and estimated that only 15 000 deaths, or approximately 4% of the total, were due to poor diet and inactivity alone. The authors did not provide a description of the methods they used to arrive at the number of 15 000.

Normal-weight persons may die because they eat too much saturated fat or are sedentary. In our study, 8.7% of deaths were in normal-weight men with elevated cholesterol levels,[4] and investigators from Sweden reported that 10.6% of deaths in their cohort occurred in normal-weight men who were sedentary.[5] Physical inactivity and poor dietary habits are important independent mortality predictors that result in adverse health effects far beyond those mediated by overweight.

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1. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA*. 2004;291:1238-1245.
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In Reply: Dr Anstadt raises the issue of beneficial effects of low-level alcohol consumption. While we agree that analysis of a U-shaped dose-response impact of alcohol on mortality would be of interest, such analysis could be more difficult for nutrition where a minimal dose is necessary for health. Thus, we chose to assess the adverse consequences of alcohol abuse rather than the potential harms and benefits associated with any alcohol use. This is similar to recommendations of the World Health Association to monitor harms from medium- and high-risk drinking.[1] Moreover, it is consistent with alcohol policy

goals in the United States, which focus on reducing excessive drinking among adults who consume alcohol.[2,3]

We agree with Dr Gandjour that it is important to consider the contribution of conditions that may not cause mortality but have significant health effects. A key question is whether prevention saves money (sometimes) and leads to better later health at less cost (often), compared with curative care. This is further complicated by the perception that prevention is a waste of money for those on whom it does not work.

In response to Drs Barnoya and Glantz, we agree that the risk of death from obesity declines with age. We disagree, however, that this significantly modifies the effect. The largest increase in the United States age distribution is in the 45- to 64-year-old age groups, which had a large increase in obesity.[4] However, the relative risks for our obesity computation were adjusted for age, sex, and smoking status,[5] and the data sources were based on prospective studies with ages ranging from 16 to 94 years at baseline. In fact, one of the surveys used is nationally representative, with an oversample of older Americans and minorities.[6] Furthermore, we explicitly discussed the possible impact of genetics; thus, we reported that our estimate for poor diet and physical inactivity was conservative.

We agree with Drs Lutfiyya and Henley that consideration of health determinants is critical in addressing these risk factors and, thus, we emphasized the importance of community policy in our article.

Finally, we agree with Dr Blair and colleagues that a normal-weight person may not be physically active or eat a balanced diet rich in fruits and vegetables and, on the other hand, that an overweight person may practice such beneficial behaviors. We also agree that poor diet and physical inactivity are associated with mortality independently of body mass index—the World Health Organization reported that an 18.5% rate of mortality in the US is attributed to poor diet and physical inactivity (8.4% attributed to BMI; 5.3% to low consumption of fruits and vegetables; and 4.8% to physical inactivity).[7] We acknowledged that our methodology may have underestimated the effects of poor diet and physical inactivity on mortality. However, we contend that obesity has made the 2 risk behaviors of poor diet and physical inactivity more visible, thereby allowing public health professionals at the medical and population level to intervene. Moreover, body weight and height are easier to measure than physical activity and diet. We agree that it is critical to promote a balanced diet and increased physical activity.

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Hypertonic Saline for Prehospital Treatment of Traumatic Brain Injury

To the Editor: Dr Cooper and colleagues[1] found no benefit to prehospital administration of 250 mL of 7.5% hypertonic saline among patients with hypotension and severe traumatic brain injury. It is not clear, however, whether the trial had sufficient statistical power to detect a meaningful difference. The trial was designed to detect a 20% improvement in the conventional extended Glasgow Outcome Score (GOSE) with 80% power and an α statistical value of .05. I do not think this is an ideal end point because I believe that most clinicians and patients would not view a change from death to persistent vegetative state or from persistent vegetative to severe disability as a treatment success.

A more important outcome would be the attainment of a functional neurological status. Other recent trials of brain injury have measured the proportion of patients with a favorable neurological outcome as the primary outcome. Given that in a recent trial of hypothermia in severe traumatic brain injury[2] in which 43% of patients attained a favorable outcome, a considerably larger number of patients would be necessary to detect difference in this end point.

I have 2 other concerns about this study. First, it is possible that the higher level of sodium at presentation among patients who received hypertonic saline could have unblinded the attending physicians and potentially affected the rates of cointerventions. The authors in fact provided little information on the in-hospital management of these patients. As in the study of Clifton et al,[3] a strict protocol should have been applied and compliance assessed.

Second, it would be of interest to know whether other known prognostic factors for severe traumatic brain injury were balanced between the groups including pupillary response (not presented), episodes of hypoxemia, episodes of hypotension, and proportion of patients in each Marshall category.

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